

Harris 09/847,356

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(FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
09:42:41 ON 23 OCT 2002)

L25 21 DUP REM L24 (24 DUPLICATES REMOVED)

=> d que 125

L1 10757 SEA MORRIS D?/AU
L2 4861 SEA THOMPSON B?/AU
L3 1363 SEA COFFEY M?/AU
L4 4222 SEA RAS(5A) (NEOPLAS? OR TUMOR# OR TUMOUR# OR CARCINOMA# OR
CANCER?) (5A) CELL#
L5 11631 SEA REOVIRUS?
L10 11 SEA ((L1 OR L2 OR L3)) AND L4
L11 16 SEA L4 AND L5
L12 179 SEA L5 (5A) (NEOPLAS? OR TUMOR# OR TUMOUR# OR CARCINOMA# OR
CANCER?)
L13 76 SEA L12 AND (TREAT? OR THERAP?)
L14 10 SEA L13 AND (ONCOLYSIS OR LYSIS OR LYSE#)
L15 28 SEA L5 (5A) RAS
L16 9 SEA (TRANSPLANT? OR IMPLANT?) AND RAS AND L5
L17 94 SEA (TRANSPLANT? OR IMPLANT?) AND L5
L18 51 SEA L17 AND (TREAT? OR THERAP?)
L19 2 SEA L18 AND (ONCOLYSIS OR LYSIS OR LYSE#)
L20 64375 SEA (TRANSPLANT? OR IMPLANT?) (5A) AUTOLOG?
L21 0 SEA L20 AND L5
L22 1882 SEA (HEMATOPOIETIC(3A) STEM OR BONE(3A) MARROW# OR BLOOD OR
LIVER# OR HEPATIC OR KIDNEY# OR HEART# OR CARDIO? OR CORNEA#
OR SKIN# OR LUNG# OR PULMON? OR PANCREA? OR SEMEN OR EGG# OR
OVA OR OVUM) AND L5
L23 6 SEA L22 AND RAS
L24 45 SEA L10 OR L11 OR L14 OR L15 OR L16 OR L19 OR L21 OR L23
L25 21 DUP REM L24 (24 DUPLICATES REMOVED)

=> d ibib abs 125 1-21

L25 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:368769 HCAPLUS
DOCUMENT NUMBER: 136:363824
TITLE: *Reovirus-based methods for the treatment of
cellular proliferative disorders*
INVENTOR(S): Coffey, Matthew C.
PATENT ASSIGNEE(S): Oncolectics Biotech, Inc., Can.
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002039117	A1	20020516	WO 2001-CA1512	20011026
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,				

Search completed by David Schreiber 308-4292

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UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002012022 A5 20020521 AU 2002-12022 20011026
US 2002086284 A1 20020704 US 2001-985756 20011106

PRIORITY APPLN. INFO.: US 2000-246728P P 20001109
WO 2001-CA1512 W 20011026

AB The invention relates to methods of identifying the susceptibility of cells to **reovirus** infection by measuring constitutive **ras**-MAP signaling. The invention also pertains to methods using a **reovirus** for the treatment of cellular proliferative disorders, and particularly cellular proliferative disorders wherein the proliferating cells exhibit constitutive MAPK phosphorylation in mammals. In particular, the methods provide for **reovirus** treatment of mammals to treat proliferative disorders which include breast tumors, a subset of tumors in which mutation of the **ras** gene is not believed to play a significant role.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:183803 BIOSIS

DOCUMENT NUMBER: PREV200200183803

TITLE: Reovirus for the treatment of neoplasia.

AUTHOR(S): Lee, Patrick W. K. (1); Strong, James; Coffey, Matthew C.

CORPORATE SOURCE: (1) Calgary Canada

ASSIGNEE: Oncolytics Biotech, Inc., Calgary, Canada

PATENT INFORMATION: US 6344195 February 05, 2002

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Feb. 5, 2002) Vol. 1255, No. 1, pp. No Pagination. <http://www.uspto.gov/web/menu/patdata.html>. e-file.

ISSN: 0098-1133.

DOCUMENT TYPE: Patent

LANGUAGE: English

AB Methods for treating neoplasia, by administering **reovirus** to a **Ras**-mediated neoplasm, are disclosed. The **reovirus** is administered so that it ultimately directly contacts cells of the neoplasm. Human reovirus, non-human mammalian reovirus, and/or avian reovirus can be used. If the reovirus is human reovirus, type 1 (e.g., strain Lang), type 2 (e.g., strain Jones), type 3 (e.g., strain Dearing or strain Abney), as well as other serotypes or strains of reovirus can be used. Combinations of more than one type and/or strain of reovirus can be used, as can reovirus from different species of animal. Either solid neoplasms or hematopoietic neoplasms can be treated.

L25 ANSWER 3 OF 21 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2002179316 MEDLINE

DOCUMENT NUMBER: 21909300 PubMed ID: 11912142

TITLE: Oncolytic **reovirus** against ovarian and colon cancer.

AUTHOR: Hirasawa Kensuke; Nishikawa Sandra G; Norman Kara L; Alain Tommy; Kossakowska Anna; Lee Patrick W K

CORPORATE SOURCE: Cancer Biology Research Group and Department of Microbiology and Infectious Diseases, University of Calgary, Calgary, Alberta, T2N 4N1 Canada.

SOURCE: CANCER RESEARCH, (2002 Mar 15) 62 (6) 1696-701.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020326
Last Updated on STN: 20020430
Entered Medline: 20020429

AB **Reovirus** selectively replicates in and destroys **cancer cells** with an activated **Ras** signaling pathway. In this study, we evaluated the feasibility of using **reovirus** (serotype 3, strain Dearing) as an antihuman colon and ovarian cancer agent. In *in vitro* studies, **reovirus** infection in human colon and ovarian cell lines was assessed by cytopathic effect as detected by light microscopy, [(35)S]Methionine labeling of infected cells for viral protein synthesis and progeny virus production by plaque assay. We observed that **reovirus** efficiently infected all five human colon cancer cell lines (Caco-2, DLD-1, HCT-116, HT-29, and SW48) and four human ovarian cancer cell lines (MDA-H2774, PA-1, SKOV3, and SW626) which were tested, but not a normal colon cell line (CCD-18Co) or a normal ovarian cell line (NOV-31). We also observed that the **Ras** activity in the human colon and ovarian cancer cell lines was elevated compared with that in normal colon and ovarian cell lines. In animal models, intraneoplastic as well as i.v. inoculation of **reovirus** resulted in significant regression of established s.c. human colon and ovarian tumors **implanted** at the hind flank. Histological studies revealed that **reovirus** infection *in vivo* was restricted to tumor cells, whereas the surrounding normal tissue remained uninfected. Additionally, in an i.p. human ovarian cancer xenograft model, inhibition of ascites tumor formation and the survival of animals treated with live **reovirus** was significantly greater than of control mice treated with UV-inactivated **reovirus**. **Reovirus** infection *in ex vivo* primary human ovarian tumor surgical samples was also confirmed, further demonstrating the potential of **reovirus** therapy. These results suggest that **reovirus** holds promise as a novel agent for human colon and ovarian cancer therapy.

L25 ANSWER 4 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:395709 BIOSIS
DOCUMENT NUMBER: PREV200200395709
TITLE: The molecular basis of **Ras**-dependent **reovirus** oncolysis.
AUTHOR(S): Norman, Kara L. (1); Yang, An-Dao (1); Hirasawa, Kensuke (1); Lee, Patrick W. K. (1)
CORPORATE SOURCE: (1) University of Calgary, Calgary, AB Canada
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 664. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 5 OF 21 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002184133 MEDLINE
DOCUMENT NUMBER: 21914443 PubMed ID: 11916487
TITLE: **Reovirus oncolysis of human breast cancer.**

AUTHOR: Norman Kara L; Coffey Matthew C; Hirasawa Kensuke;
Demetrick Douglas J; Nishikawa Sandra G; DiFrancesco Lisa
M; Strong James E; Lee Patrick W K

CORPORATE SOURCE: Cancer Biology Research Group, Faculty of Medicine,
University of Calgary, Calgary, Alberta, T2N 4N1 Canada.

SOURCE: HUMAN GENE THERAPY, (2002 Mar 20) 13 (5) 641-52.
Journal code: 9008950. ISSN: 1043-0342.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200206

ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020626
Entered Medline: 20020625

AB We have previously shown that human **reovirus** replication is restricted to cells with an activated **Ras** pathway, and that **reovirus** could be used as an effective oncolytic agent against human glioblastoma xenografts. This study examines in more detail the feasibility of **reovirus** as a **therapeutic** for breast **cancer**, a subset of cancer in which direct activating mutations in the **ras** proto-oncogene are rare, and yet where unregulated stimulation of **Ras** signaling pathways is important in the pathogenesis of the disease. We demonstrate herein the efficient **lysis** of breast tumor-derived cell lines by the virus, whereas normal breast cells resist infection in vitro. In vivo studies of **reovirus** breast **cancer therapy** reveal that viral administration could cause tumor regression in an MDA-MB-435S mammary fat pad model in severe combined immunodeficient mice. **Reovirus** could also effect regression of **tumors** remote from the injection site in an MDA-MB-468 bilateral tumor model, raising the possibility of systemic **therapy** of breast cancer by the oncolytic agent. Finally, the ability of **reovirus** to act against primary breast **tumor** samples not propagated as cell lines was evaluated; we found that **reovirus** could indeed replicate in ex vivo surgical specimens. Overall, **reovirus** shows promise as a potential breast cancer **therapeutic**.

L25 ANSWER 6 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002287340 EMBASE

TITLE: The potential of gene therapy in the treatment of **pancreatic** cancer.

AUTHOR: Kasuya H.; Nomoto S.; Nakao A.

CORPORATE SOURCE: Dr. H. Kasuya, Department of Surgery II, University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. kasuya@helix.mgh.harvard.edu

SOURCE: Drugs of Today, (2002) 38/7 (457-464).
Refs: 55
ISSN: 0025-7656 CODEN: MDACAP

COUNTRY: Spain

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Pancreatic** cancer is known to be one of the most problematic forms of cancer. Researchers around the world are still trying to find an adequate treatment for this disease. While surgical operation has been the

dominant procedure for treating **pancreatic** cancer, adjuvant therapies such as radiation or chemotherapy (although the survival rate is still poor) also exist. **Pancreatic** cancer is notoriously difficult to detect at its initial invasion, despite modern radiographic technology. This means that patients discover the cancer when it is already in an advanced stage, making surgical resection difficult. A new strategy for medical practice in **pancreatic** cancer is much needed. Gene therapy is currently in the spotlight as a promising new method for cancer cure. Many studies have revealed the potential of this therapy for the treatment of **pancreatic** cancer, and early clinical trials are taking place to evaluate the success of gene therapy regimes in humans. Here we discuss basic scientific principles and clinical experience with respect to these regimes, including antisense strategies, gene-directed prodrug activation therapy, promoter-gene strategies and oncolytic viral therapy. .COPYRGT. 2002 Prous Science. All rights reserved.

L25 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2002:262426 HCAPLUS
 TITLE: **Reovirus** therapy of **Ras**-associated cancers
 AUTHOR(S): Lee, Patrick W. K.
 CORPORATE SOURCE: Cancer Biology Research Group and Department of Microbiology and Infectious Diseases Faculty of Medicine, University of Calgary, Calgary, AB, T2N 4N1, Can.
 SOURCE: Tumor-Suppressing Viruses, Genes, and Drugs (2002), 31-43. Editor(s): Maruta, Hiroshi. Academic Press: San Diego, Calif.
 DOCUMENT TYPE: Conference; General Review
 LANGUAGE: English
 AB A review, discussing the studies on the structural and functional anal. of the reovirus proteins encoded by the ten gene segments. Among the reovirus proteins, the S1 gene product is the most thoroughly studied, probably because it is the cell attachment protein and therefore plays a major role in tissue tropism. (c) 2002 Academic Press.
 REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
 ACCESSION NUMBER: 2001:516239 HCAPLUS
 TITLE: Reovirus for the treatment of neoplasia
 INVENTOR(S): Lee, Patrick W. K.; Strong, James; Coffey, Matthew C.
 PATENT ASSIGNEE(S): Oncolectics Biotech, Inc., Can.
 SOURCE: U.S., 16 pp., Cont.-in-part of Ser. No. US 1997-911383, filed on 13 Aug 1997, now
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6261555	B1	20010717	US 2000-485390	20000518
EP 1003534	A1	20000531	EP 1998-940002	19980812
EP 1003534	B1	20020306		

R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC,
NL, PT, SE
AT 213948 E 20020315 AT 1998-940002 19980812
JP 2002511886 T2 20020416 JP 1999-512590 19980812
EP 1213023 A1 20020612 EP 2001-130285 19980812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI, CY
US 2001048920 A1 20011206 US 2001-852017 20010510
PRIORITY APPLN. INFO.: US 1997-911383 A2 19970813
WO 1998-CA774 W 19980812
EP 1998-940002 A3 19980812
US 2000-485390 A3 20000518

AB Methods for treating neoplasia, by administering **reovirus** to a **Ras**-mediated neoplasm, and use of **reovirus** for manufacture of a medicament for the treatment of neoplasia, are disclosed. The reovirus is administered so that it ultimately directly contacts cells of the neoplasm. Human reovirus, non-human mammalian reovirus, and/or avian reovirus can be used. If the reovirus is human reovirus, type 1 (e.g., strain Lang), type 2 (e.g., strain Jones), type 3 (e.g., strain Dearing or strain Abney), as well as other serotypes or strains of reovirus can be used. Combinations of more than one type and/or strain of reovirus can be used, as can reovirus from different species of animal. Either solid neoplasms or hematopoietic neoplasms can be treated.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:813370 HCAPLUS

TITLE: **Reovirus** clearance of **ras**-mediated neoplastic cells from mixed cellular compositions

INVENTOR(S): Morris, Donald; Thompson, Bradley G.; Coffey, Matthew C.

PATENT ASSIGNEE(S): Oncolytics Biotech, Inc., Can.

SOURCE: PCT Int. Appl.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083711	A2	20011108	WO 2001-CA620	20010502
WO 2001083711	A3	20020510		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002006398	A1	20020117	US 2001-847356	20010503
PRIORITY APPLN. INFO.:			US 2000-201990P	P 20000503
			US 2000-205389P	P 20000519
			US 2001-268054P	P 20010213

AB **Reovirus** can be used to selectively remove **ras**

-mediated neoplastic cells from a cellular composition. It is of particular interest to purge autographs which may contain neoplastic cells with **reovirus** before transplanting the autografts back into the recipient, thereby reducing the risk of introducing or reintroducing neoplastic cells into the recipient.

L25 ANSWER 10 OF 21 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001352128 MEDLINE
DOCUMENT NUMBER: 21309242 PubMed ID: 11416111
TITLE: **Reovirus** as an oncolytic agent against experimental human malignant gliomas.
COMMENT: Comment in: J Natl Cancer Inst. 2001 Jun 20;93(12):889-90
AUTHOR: Wilcox M E; Yang W; Senger D; Newcastle N B; Morris D G; Brasher P M; Shi Z Q; Johnston R N; Nishikawa S; Lee P W; Forsyth P A
CORPORATE SOURCE: Departments of Oncology and Clinical Neurosciences, University of Calgary, and Tom Baker Cancer Centre, Alberta, Canada.
SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE, (2001 Jun 20) 93 (12) 903-12.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB BACKGROUND: **Reovirus** is a naturally occurring oncolytic virus that usurps activated **Ras**-signaling pathways of **tumor cells** for its replication. **Ras** pathways are activated in most malignant gliomas via upstream signaling by receptor tyrosine kinases. The purpose of this study was to determine the effectiveness of **reovirus** as an experimental **treatment** for malignant gliomas. METHODS: We investigated whether **reovirus** would infect and **lyse** human glioma cell lines *in vitro*. We also tested the effect of injecting live **reovirus** *in vivo* on human gliomas grown subcutaneously or orthotopically (i.e., intracerebrally) in mice. Finally, **reovirus** was tested *ex vivo* against low-passage cell lines derived from human glioma specimens. All P values were two-sided. RESULTS: **Reovirus** killed 20 (83%) of 24 established malignant glioma cell lines tested. It caused a dramatic and often complete tumor regression *in vivo* in two subcutaneous ($P = .0002$ for both U251N and U87) and in two intracerebral ($P = .0004$ for U251N and $P = .0009$ for U87) human malignant glioma mouse models. As expected, serious toxic effects were found in these severely immunocompromised hosts. In a less immunocompromised mouse model, a single intratumoral inoculation of live **reovirus** led to a dramatic prolongation of survival (compared with control mice **treated** with dead virus; log-rank test, $P < .0001$ for both U251N and U87 cell lines). The animals **treated** with live virus also appeared to be healthier and gained body weight ($P = .0001$). We then tested the ability of **reovirus** to infect and kill primary cultures of brain tumors removed from patients and found that it killed nine (100%) of nine glioma specimens but none of the cultured meningiomas. CONCLUSIONS: **Reovirus** has potent activity against human malignant gliomas *in vitro*, *in vivo*, and *ex vivo*. **Oncolysis with reovirus** may be a potentially useful **treatment** for a broad range of human

cancers.

L25 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
 ACCESSION NUMBER: 2000:752081 HCAPLUS
 DOCUMENT NUMBER: 133:313603
 TITLE: **Reovirus for the treatment of cellular proliferative disorders**
 INVENTOR(S): Lee, Patrick W. K.; Strong, James; Coffey, Matthew C.
 PATENT ASSIGNEE(S): OncoLytics Biotech Inc., Can.
 SOURCE: U.S., 22 pp., Cont.-in-part of U.S. Ser. No. 911,383.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6136307	A	20001024	US 1999-256824	19990224
EP 1213023	A1	20020612	EP 2001-130285	19980812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
WO 2000050051	A2	20000831	WO 2000-CA178	20000218
WO 2000050051	A3	20001228		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1156813	A2	20011128	EP 2000-906094	20000218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6344195	B1	20020205	US 2000-569865	20000512
US 6455038	B1	20020924	US 2000-594343	20000615
PRIORITY APPLN. INFO.: US 1997-911383 A2 19970813 EP 1998-940002 A3 19980812 US 1999-256824 A1 19990224 WO 2000-CA178 W 20000218				

AB Methods for **treating** proliferative disorders, by administering **reovirus** to a **Ras**-mediated proliferative disorder, are disclosed. The **reovirus** is administered so that it ultimately directly contacts **ras**-mediated proliferating cells. Proliferative disorders include but are not limited to neoplasms. Human **reovirus**, non-human mammalian **reovirus**, and/or avian **reovirus** can be used. If the **reovirus** is human **reovirus**, serotype 1 (e.g., strain Lang), serotype 2 (e.g., strain Jones), serotype 3 (e.g., strain Dearing or strain Abney), as well as other serotypes or strains of **reovirus** can be used. Combinations of more than one type and/or strain of **reovirus** can be used, as can **reovirus** from different species of animal. Either solid neoplasms or hematopoietic neoplasms can be **treated**.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:606961 HCAPLUS
TITLE: Reovirus for the treatment of cellular proliferative disorders
INVENTOR(S): Lee, Patrick W. K.; Strong, James; Coffey, Matthew C.
PATENT ASSIGNEE(S): Oncolytics Biotech, Inc., Can.
SOURCE: PCT Int. Appl.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050051	A2	20000831	WO 2000-CA178	20000218
WO 2000050051	A3	20001228		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6136307	A	20001024	US 1999-256824	19990224
EP 1156813	A2	20011128	EP 2000-906094	20000218
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRIORITY APPLN. INFO.:			US 1999-256824	A1 19990224
			US 1997-911383	A2 19970813
			WO 2000-CA178	W 20000218

AB Methods for treating proliferative disorders, by administering **reovirus** to a **Ras**-mediated proliferative disorder, are disclosed. The reovirus is administered so that it ultimately directly contacts ras-mediated proliferating cells. Proliferative disorders include but are not limited to neoplasms. Human reovirus, non-human mammalian reovirus, and/or avian reovirus can be used. If the reovirus is human reovirus, serotype 1 (e.g., strain Lang), serotype 2 (e.g., strain Jones), serotype 3 (e.g., strain Dearing or strain Abney), as well as other serotypes or strains of reovirus can be used. Combinations of more than one type and/or strain of reovirus can be used, as can reovirus from different species of animal. Either solid neoplasms or hematopoietic neoplasms can be treated.

L25 ANSWER 13 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:202897 BIOSIS
DOCUMENT NUMBER: PREV200100202897
TITLE: Reovirus for the treatment of neoplasia.
AUTHOR(S): Lee, Patrick W. K. (1); Strong, James; Coffey, Matthew C.
CORPORATE SOURCE: (1) N. W. Calgary Canada
ASSIGNEE: Oncolytics Biotech Inc., Calgary, Canada
PATENT INFORMATION: US 6110461 August 29, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 29, 2000) Vol. 1237, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.

DOCUMENT TYPE: Patent
LANGUAGE: English

AB Methods for treating neoplasia, by administering **reovirus** to a **Ras**-mediated neoplasm, are disclosed. The **reovirus** is administered so that it ultimately directly contacts cells of the neoplasm. Human reovirus, non-human mammalian reovirus, and/or avian reovirus can be used. If the reovirus is human reovirus, type 1 (e.g., strain Lang), type 2 (e.g., strain Jones), type 3 (e.g., strain Dearing or strain Abney), as well as other serotypes or strains of reovirus can be used. Combinations of more than one type and/or strain of reovirus can be used, as can reovirus from different species of animal. Either solid neoplasms or hematopoietic neoplasms can be treated.

L25 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:238476 BIOSIS

DOCUMENT NUMBER: PREV200000238476

TITLE: Study of **reovirus**-induced cytopathic effect (CPE), **ras** and double-stranded RNA-activated protein kinase (PKR) in human tumor cell lines.

AUTHOR(S): Song, L.-T. (1); Gelman, I. (1); Holland, J. F. (1); Ohuma, T. (1)

CORPORATE SOURCE: (1) Mount Sinai Sch of Medicine, New York, NY USA

SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 350.

Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000

ISSN: 0197-016X.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L25 ANSWER 15 OF 21 MEDLINE

DUPLICATE 6

ACCESSION NUMBER: 2001034604 MEDLINE

DOCUMENT NUMBER: 20516007 PubMed ID: 11060679

TITLE: Oncolytic viruses as novel anticancer agents: turning one scourge against another.

AUTHOR: Smith E R; Chiocca E A

CORPORATE SOURCE: Molecular Neuro-oncology Laboratories, Neurosurgery Service, Massachusetts General Hospital, CNY6, 13th Street, Charlestown, MA 02119, USA.

SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2000 Feb) 9 (2) 311-27. Ref: 140

Journal code: 9434197. ISSN: 1354-3784.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200011

ENTRY DATE: Entered STN: 20010322

Last Updated on STN: 20010322

Entered Medline: 20001130

AB Although the use of viruses as oncolytic agents is an historic concept, the use of genetically modified viruses to selectively target tumour cells is relatively novel and recent. The ability of viruses to efficiently infect and **lyse** cells, combined with the potential augmentation of this effect by progeny viruses throughout the tumour provide

justification for exploitation of these agents in cancer **therapy**. Before application to humans, though, issues related to tumour cell selectivity, lack of toxicity to normal tissues and the effect of the antiviral immune response, will have to be clarified. The more commonly used oncolytic viruses are based on mutant strains of herpes simplex virus, adenovirus and **reovirus**. The **tumour** selectivity of each of these strains is discussed, particularly the complementation of the viral defect by cellular pathways involved in tumourigenesis. The combination of oncolytic viruses with radiation, chemotherapy and gene **therapy** is also reviewed. Further study of the interaction of viral proteins with cellular pathways involved in cell cycle control will provide the rationale for viral mutants with increased selectivity for tumour cells.

L25 ANSWER 16 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999404644 EMBASE
TITLE: Concepts in **Ras**-directed therapy.
AUTHOR: Kloog Y.; Cox A.D.; Sinensky M.
CORPORATE SOURCE: Y. Kloog, Department of Neurobiochemistry, George S. Wise Faculty Life Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel. kloog@ccsg.tau.ac.il
SOURCE: Expert Opinion on Investigational Drugs, (1999) 8/12 (2121-2140).
Refs: 173
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Ras** proteins are key transducers of growth signals regulated by cell surface receptors. They are anchored to the inner surface of the cell membrane where receptor-mediated signalling induces **Ras** activation (GDP/GTP exchange) and inactivation (stimulation of **Ras** GTPase activity). **Ras**-GTP in turn activates a multitude of signalling cascades controlling cell growth and differentiation. Aberrant **Ras** function (mostly constitutive activation) contributes to the development of many types of neoplastic human diseases. Activating mutations in **ras** genes, leading to the expression of **Ras** proteins insensitive to **Ras**-GTPase activating proteins, are found in as many as 30% of all human tumours. This suggests that **Ras** is an appropriate target for drug design. Remarkable improvements in the understanding of post-translational modifications in **Ras** that promote **Ras**-membrane anchorage, in the mechanisms of activation and inactivation of **Ras**, and in the interactions of **Ras** with a plethora of effector molecules have led to the development of new concepts for **Ras**-directed therapy. The most advanced approach has been that of farnesyltransferase inhibitors (FTIs) designed to inhibit the farnesylation of **Ras** required for membrane anchorage and transforming activity. FTIs now in clinical trials have been extensively reviewed. Here we review the progress in the development of FTIs and in the development of other promising concepts for **Ras**-directed therapy. These include compounds such as S-farnesylthiosalicylic acid (FTS), which disrupt the proper anchorage of **Ras** with the cell membrane acid inhibit human tumour growth in animal models, and compounds that interfere with interactions of **Ras** with its downstream effectors. We conclude with a description

of a recently described novel drug concept that could restore the defective GTPase activity of oncogenic **Ras** and with the interesting results of **reovirus**-induced tumour regression observed in animal models of human tumours containing an intact **Ras** signalling pathway.

L25 ANSWER 17 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999148477 EMBASE
TITLE: Modulation of the immune response and tumor growth by activated **Ras**.
AUTHOR: Weijzen S.; Velders M.P.; Kast W.M.
CORPORATE SOURCE: W.M. Kast, Cancer Immunology Program, Cardinal Bernardin Cancer Center, Loyola University Chicago, 2160 South First Avenue, Maywood, IL 60153, United States
SOURCE: Leukemia, (1999) 13/4 (502-513).
Refs: 107
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB As a result of its transforming abilities, activated **Ras** is expressed in a great number of cancers. The **ras** mutation frequency varies between 95% in **pancreatic** cancer and 5% in breast cancer. In leukemia, the highest frequency (30%) is found in acute myeloid leukemia. The presence of **ras** mutations has been correlated with a poor prognosis and negative clinical outcome. This suggests that mutated **Ras** activates mechanisms, which favor tumor growth, enhance the metastatic capacity of tumors or modulate tumor-specific immune responses. Several new functions of **Ras**, such as downregulation of major histocompatibility complex molecules, upregulation of certain cytokines, growth factors and degradative enzymes have been uncovered in the last decade. Additionally, mutated **Ras** can also serve as a primary target for the development of immunotherapy or drug therapy. This review will discuss the mechanisms by which **Ras** expressing tumors are able to evade destruction by the immune system and enhance their growth and metastatic potential. It will further elaborate on the attempts to develop successful immunotherapy and drug therapy targeting **Ras** expressing tumors.

L25 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:242127 BIOSIS
DOCUMENT NUMBER: PREV199900242127
TITLE: Oncolysis and tumor regression with **reovirus** in a malignant glioma model.
AUTHOR(S): Wilcox, M. Elizabeth (1); Coffey, Matthew (1); Strong, James (1); Shi, Qiao (1); Newcastle, N. Barry (1); Brasher, Penny M. (1); Lee, Patrick W. K.; Forsyth, Peter (1)
CORPORATE SOURCE: Univ. Calgary, Tom Baker Cancer Cent., Calgary, Alberta Canada
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 421.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer

Research
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 19 OF 21 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998292455 MEDLINE
DOCUMENT NUMBER: 98292455 PubMed ID: 9628872
TITLE: The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by **reovirus**.
AUTHOR: Strong J E; Coffey M C; Tang D; Sabinin P; Lee P W
CORPORATE SOURCE: Department of Microbiology and Infectious Diseases,
University of Calgary Health Sciences Centre, Calgary,
Alberta, Canada T2N 4N1.
SOURCE: EMBO JOURNAL, (1998 Jun 15) 17 (12) 3351-62.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980730
AB NIH-3T3 cells, which are resistant to reovirus infection, became susceptible when transformed with activated Sos or Ras. Restriction of **reovirus** proliferation in untransformed NIH-3T3 cells was not at the level of viral gene transcription, but rather at the level of viral protein synthesis. An analysis of cell lysates revealed that a 65 kDa protein was phosphorylated in untransformed NIH-3T3 cells, but only after infection with reovirus. This protein was not phosphorylated in infected or uninfected transformed cells. The 65 kDa protein was determined to be the double-stranded RNA-activated protein kinase (PKR), whose phosphorylation leads to translation inhibition. Inhibition of PKR phosphorylation by 2-aminopurine, or deletion of the Pkr gene, led to drastic enhancement of reovirus protein synthesis in untransformed cells. The emerging picture is one in which early viral transcripts trigger PKR phosphorylation in untransformed cells, which in turn leads to inhibition of translation of viral genes; this phosphorylation event is blocked by an element(s) in the Ras pathway in the transformed cells, allowing viral protein synthesis to ensue. The usurpation of the Ras signaling pathway therefore constitutes the basis of reovirus oncolysis.

L25 ANSWER 20 OF 21 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999030699 MEDLINE
DOCUMENT NUMBER: 99030699 PubMed ID: 9812900
TITLE: **Reovirus** therapy of tumors with activated Ras pathway.
COMMENT: Comment in: Science. 1998 Nov 13;282(5392):1244-6
AUTHOR: Coffey M C; Strong J E; Forsyth P A; Lee P W
CORPORATE SOURCE: Cancer Biology Research Group and Department of Microbiology and Infectious Diseases, University of Calgary Health Science Centre, Calgary, Alberta, T2N 4N1, Canada.
SOURCE: ✓ SCIENCE, (1998 Nov 13) 282 (5392) 1332-4. (DS)
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981201

AB Human **reovirus** requires an activated **Ras** signaling pathway for infection of cultured cells. To investigate whether this property can be exploited for cancer therapy, severe combined immune deficient mice bearing tumors established from v-erbB-transformed murine NIH 3T3 cells or human U87 glioblastoma cells were treated with the virus. A single intratumoral injection of virus resulted in regression of tumors in 65 to 80 percent of the mice. Treatment of immune-competent C3H mice bearing **tumors** established from **ras**-transformed C3H-10T1/2 **cells** also resulted in tumor regression, although a series of injections were required. These results suggest that, with further work, **reovirus** may have applicability in the treatment of cancer.

L25 ANSWER 21 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:107782 BIOSIS
DOCUMENT NUMBER: PREV199698679917
TITLE: Mechanism of interferon action: Biochemical and genetic evidence for the intermolecular association of the RNA-dependent protein kinase PKR from human cells.
AUTHOR(S): Ortega, Laura G.; McCotter, Matthew D.; Henry, Gilbert L.; McCormack, Stephen J.; Thomis, Daniel C.; Samuel, Charles E. (1)
CORPORATE SOURCE: (1) Dep. Mol. Cellular Dev. Biol., Interdepartmental Biochemistry, Univ. California, Santa Barbara, CA 93106 USA
SOURCE: Virology, (1996) Vol. 215, No. 1, pp. 31-39.
ISSN: 0042-6822.

DOCUMENT TYPE: Article
LANGUAGE: English

AB The interferon-inducible protein kinase (PKR) is activated by an RNA-dependent autophosphorylation. Structure-function studies of the 551 amino acid PKR kinase from human cells have revealed that catalytic-deficient PKR mutants such as PKR(1-551)K296R display a dominant negative behavior when expressed in transfected cells. The potential for PKR to form protein multimers has therefore been examined. Three types of studies, including both genetic and biochemical analyses, demonstrated that PKR from human cells undergoes an intermolecular association that is not dependent upon RNA. First, the intermolecular association of PKR *in vitro* was demonstrated in the context of an enzyme-substrate interaction. Purified recombinant histidine-tagged PKR(1 -551)K296R mutant protein was phosphorylated by purified wild-type PKR; this intermolecular phosphorylation of PKR was dependent on double-stranded RNA. At a fixed RNA concentration, high concentrations of the HIS-PKR(1 -551)K296R mutant both impaired the autophosphorylation of wild-type PKR and blocked the trans-phosphorylation of itself. Second, the yeast two-hybrid system was used to probe the intermolecular association of PKR *in vivo*. Coexpression of the full-length catalytic-deficient phosphotransfer mutant PKR(1 -551)K296R as a fusion protein with the Gal4 activation domain and the Gal4 DNA binding domain resulted in the expression of two Gal4-responsive reporter genes, HIS3 and lacZ. The full-length RNA-binding deficient PKR(1-551)K64E/K296R double mutant also interacted with PKR(1 551)K296R sufficiently to activate Gal4-responsive reporter genes; however, other PKR mutants including PKR(1-280)wt and PKR(281-551)K296R as well as p53, RAS, and BCL2 did not. Third, both PKR(1 -551)K296R and PKR(1 -551)K64E/K296R enhanced the expression of the **reovirus** S1 gene

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and S1/S4 chimeric gene in cotransfected COS cells. By contrast, the expression of the **reovirus** S4 gene was not enhanced by cotransfection with either PKR(1 -551)K296R or PKR(1 -551)K64E/ K296R. These results indicate that PKR interacts with itself in an intermolecular manner both *in vivo* and *in vitro*, and that RNA binding is neither necessary nor sufficient for PKR multimerization.